



## Local delivery of chemotherapeutic agents in periodontal therapy

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### Introduction

Over the past 20 years, testing of local delivery chemotherapeutic agents as adjuncts to scaling and root planing (S/RP) and as stand alone therapies has increased. Goodson (1985) suggested that for a drug delivery system to be effective and clinically useful for periodontal therapy it must deliver the drug to the base of the pocket, reach a minimal inhibitory concentration (MIC), and sustain that concentration in the pocket for sufficient time to be effective (1). Other considerations include acceptable cost, ease of placement, retention after placement, and biodegradability of the agent (2).

The critical factor regarding effectiveness of locally delivered agents remains the length of time that microflora are exposed to the agent (3). Irrigating the pocket directly with antimicrobial solutions has been shown to provide no additional benefit over S/RP alone because sufficient concentration of the agent is probably not maintained at the target site for adequate periods of time. Metronidazole and minocycline gels, categorized as sustained local drug delivery systems, provide increased drug concentration for only 24 hours. In contrast, the chlorhexidine chip and doxycycline hyclate polymers maintain steady state high drug concentrations for prolonged periods of time.

Local delivery systems marketed in the United States and Europe have demonstrated clinical results comparable to S/RP alone thus establishing a biologic rationale for their effect. However, use of the medications for monotherapy is not presently recommended as S/RP alone removes organic debris, is more economical and achieves excellent success compared to drug therapy. Table 1 compares probing depth reductions from several large clinical trials that used local drug delivery (2).

### Tetracycline impregnated fibers (Actisite®)

Goodson et al., attempting to utilize controlled local drug delivery for the management of periodontitis, administered non-degradable ethylene vinyl acetate fibers saturated with 25% tetracycline (4). Large-scale controlled clinical trials that evaluated the efficacy of tetracycline fiber monotherapy found these fibers as effective as S/RP alone. While TCN fibers may enhance S/RP, there is no data beyond six months, which demonstrates any benefit for combined therapy at non-responsive sites (2).

### Chlorhexidine Chips (PerioChip®)

Chlorhexidine (CHX) has been used as an antiseptic mouthwash for years. Unfortunate side effects such as staining, increased calculus formation, and altered taste sensation have been noted. Chlorhexidine chips were developed to take advantage of the antimicrobial properties of CHX without the side effects associated with the rinse. Each chip, impregnated with 2.5 mg of chlorhexidine, degrades over 7-10 days but maintains a drug concentration of  $\geq 100$  ppm in the crevicular fluid. At this concentration 99% of the subgingival microflora is inhibited. Minimal side effects appear to be induced, and development of resistance to chlorhexidine is uncommon. As an adjunctive therapy, the chlorhexidine chip provides only a small clinical

benefit beyond that achieved with root planing alone. Statistically significant gains of less than 0.5mm are not clinically relevant. Deeper sites ( $\geq 7$ mm) exhibited more marked differences, yet clinical attachment gain was still less than 1mm. Combined S/RP and chip therapy resulted in the greatest number of sites with  $\geq 2$ mm probing reduction. At specific sites this amount of reduction may be clinically relevant and preclude the need for surgical intervention (5).

### Metronidazole Dental Gel 25% (Elyzol®)

Metronidazole gel, consisting of metronidazole benzolate in a mix of monoglycerides and triglycerides, is only available in Europe under the trade name - Elyzol. Studies evaluating combined treatment using Elyzol and S/RP demonstrated no adjunctive benefit. Local delivery of metronidazole should not be used as a substitute for conventional treatment of periodontal disease, as side effects of long term and repeated use are not known (6).

### Minocycline HCl 2% Ointment (Dentomycin®)

Minocycline has been used in various modes for local application including a film, microspheres, and ointment. Research focus is now centered on a 2% ointment. The drug has been applied every 2 weeks Q 3-4 application periods in conjunction with S/RP. It significantly improved microbiological and clinical parameters versus S/RP alone in adult periodontitis. The frequency of application for long-term results remains to be evaluated. Incidence of adverse events with the minocycline ointment and a placebo treatment were identical. In two large controlled clinical studies the minocycline ointment formulation consistently showed significant effectiveness in reducing bacterial populations and in eliminating motile organisms. Although the use of S/RP by itself in these studies led to a dramatic improvement which masked additive effects of the agent, the results of minocycline application were significantly superior to the placebo ointment. In probing depths greater than 7mm, minocycline ointment resulted in an additional 1mm probing depth reduction over S/RP alone. A 1mm gain in clinical attachment may result in conservative non-surgical therapy vice surgical intervention. Limitations to the use of both of minocycline and metronidazole include the number of required applications, making these agents inconvenient and time consuming to use (7).

### 10% Doxycycline Hyclate Polymer (Atridox®)

Atridox, a locally delivered doxycycline hyclate, is suspended in a bioresorbable poly-lactide. The gel formulations reach over 1200µg/ml within gingival crevicular fluid and may be sustained over a 7-8 day period. Locally administered doxycycline hyclate has been shown to produce clinical responses equivalent to that of S/RP in three large clinical trials. Atridox was shown to be significantly superior to a placebo control and equal to S/RP in pocket depth reduction and attachment gain at all time points. The system showed best effects in pockets originally  $\geq 7$ mm. Doxycycline polymer still remains to be tested as an adjunctive therapy to S/RP (8).

## Conclusion

Only one study has compared relative efficacy of the different local delivery devices (tetracycline fiber, metronidazole gel, and minocycline gel). Radvar et al, following a course of initial mechanical therapy, assessed device effects as adjuncts to S/RP in the treatment of sites with persistent periodontal lesions. While all three locally applied systems had some benefit over S/RP alone, only tetracycline fibers demonstrated a significantly greater advantage over the control therapy in the treatment of persistent periodontal lesions (9).

Results of present studies suggest that most local delivery systems appear to be capable of reducing probing depths and achieving modest gains in clinical attachment when compared to S/RP alone. Differences were statistically significant but may not be clinically significant because the clinical attachment gain was less than 0.5 mm. However, the number of sites with  $\geq 2$  mm probing reduction was greater with combined therapy. At specific sites this amount of pocket reduction may be clinically relevant and preclude the need for surgical intervention.

Overall, the data suggests that local drug deliveries result in transient selection and increased drug resistant organisms. Utilization of antibiotics via local delivery should be approached using judicious pharmacologic principles. No single universal drug is effective in all situations. Bacterial and antibiotic sensitivity testing may be necessary at non-responsive sites to identify specific antimicrobial agents that might be effective.

Sub-gingival delivery of antiseptics or antibiotics cannot be considered final, permanent, stand-alone therapies in the treatment of periodontal diseases. Since the clinical effect of S/RP is largely due to its effect in reducing the bacterial load within the periodontal pocket, it seems more likely that sub-gingival antimicrobials may be used to enhance S/RP effects (5). As mechanical instrumentation is currently effective in the treatment of adult periodontitis, it is difficult to justify combined therapy unless it clearly attains a better clinical result. Local drug delivery, as an adjunct to conventional care, should be reserved for non-responding sites or patients with recurrent disease who need an alternative treatment approach. It can be most beneficial in the control of a localized persistent lesion in otherwise stable patients.

**TABLE 1:** Comparison of probing depth reduction from several clinical trials using local drug delivery.

SYSTEM	RESEARCHER	STUDY LENGTH	S/RP	MONO-THERAPY	COMBINED THERAPY
Tetracycline fiber	Goodson et al	3 months	0.67mm	1.02mm	---
	Neuman et al	6 months	1.08mm	---	1.81 mm
Chlorhexidine chip	Jeffcoat et al	9 months	0.65mm	---	0.95 mm
Minocycline gel	Van Steenberghe et al	6 months	1.40 mm*	---	1.70 mm*
			2.10 mm**	---	3.10 mm**
Metronidazole gel	Stetzel et al	6 months	1.00 mm	1.50 mm	1.30 mm
Doxycycline polymer	Garrett et al	6 months	1.30 mm	1.30 mm	---

\* - sites with 5-6 mm probing depths

\*\* - Sites with  $\geq 7$  mm probing depths

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